IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF ILLINOIS
EASTERN DIVISION

In re: Testosterone Replacement	**)**	
Therapy Products Liability Litigation	**)**	**No. 14 C 1748**
Coordinated Pretrial Proceedings	**)**	**MDL No. 2545**
	)	
(This document applies to all cases)	**)**	

CASE MANAGEMENT ORDER NO. 46
(Rulings on AbbVie's motion to exclude expert testimony on causation and for summary judgment and plaintiffs' motion to limit testimony of Dr. Marais – dkt. 1738 & 1753)

MATTHEW F. KENNELLY, District Judge:

Plaintiffs in this multidistrict litigation (MDL) proceeding allege that they suffered either arterial cardiovascular injuries or injuries related to blood clots in the veins (venous thromboembolisms, or VTEs) as a result of taking prescription testosterone replacement therapy (TRT) drugs. Defendants AbbVie Inc., Abbott Laboratories, AbbVie Products LLC, and Unimed Pharmaceuticals, LLC (collectively, AbbVie) manufacture AndroGel,[1] one of the TRT products at issue in this litigation. Of the more than 7,000 cases consolidated in this proceeding, seven cases in which AbbVie is a defendant have been selected for bellwether trials.[2]

Plaintiffs in each of the seven cases—Edward Cribbs, Cecile Frost, Jeffrey Konrad, Jesse Mitchell, Arthur Myers, Robert Nolte, and Robert Rowley—allege that

[1] Unimed and AbbVie Products, formerly known as Solvay Pharmaceuticals, Inc., are wholly-owned subsidiaries of AbbVie Inc. AbbVie Inc. was established as an independent company from Abbott Laboratories in January 2013. Abbott Laboratories no longer sells AndroGel in the United States.

[2] The Court selected an eighth bellwether case, but the plaintiff voluntarily dismissed his lawsuit.

AndroGel caused them to suffer either a cardiovascular or a VTE injury. Following discovery, AbbVie has moved to exclude the testimony of a number of plaintiffs' proposed general and case-specific expert witnesses regarding causation under Federal Rules of Evidence 104(a), 403, 702, and 703 and *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993). AbbVie has also moved for summary judgment in each of the bellwether cases, arguing that plaintiffs lack evidence sufficient to prove that AndroGel caused their injuries. Plaintiffs, for their part, have moved to exclude the testimony of one of AbbVie's proposed expert witnesses. In this opinion, the Court addresses (1) AbbVie's motion to exclude expert testimony concerning general causation—that is, whether AndroGel is capable, in general, of causing the injuries plaintiffs allege—and specific causation—that is, whether AndroGel did indeed cause the specific injuries plaintiffs allege in their individual cases; (2) AbbVie's motion for summary judgment based on plaintiffs' purported lack of causation evidence; and (3) plaintiffs' motion to limit the testimony of Dr. M. Laurentius Marais, one of AbbVie's statistical experts. The Court grants AbbVie's motion to exclude expert testimony concerning causation in part and denies it in part. The Court also grants AbbVie's motion for summary judgment with respect to plaintiff Cribbs but otherwise denies summary judgment. In addition, the Court denies plaintiffs' motion to limit or exclude Dr. Marais' testimony.

Background

The Food and Drug Administration (FDA) has approved two different formulations of AbbVie's TRT drug AndroGel, AndroGel 1% and AndroGel 1.62%, for the treatment of male hypogonadism. The term "hypogonadism" refers generally to a

disorder characterized by abnormally low levels of testosterone in the blood and associated symptoms such as decreased libido, reduced lean body mass, decreased energy, and depressed mood. The parties dispute whether TRT is effective, and appropriately marketed, for the treatment of all forms of hypogonadism or only for so-called "classical hypogonadism," a disorder in which certain recognized medical conditions result in an absence of or deficiency in testosterone. Regarding plaintiffs' allegations that AbbVie inappropriately marketed AndroGel "off label," or for purposes other than those approved by the FDA, AbbVie has filed a separate motion for summary judgment and for exclusion of expert testimony, and the Court will issue a separate opinion addressing that motion. In addition to their assertions that TRT products are ineffective and inappropriately marketed, plaintiffs allege that TRT, including use of AndroGel, increases the risk of cardiovascular and VTE injuries. Plaintiffs Cribbs, Frost, Konrad, and Mitchell assert that they suffered cardiovascular injuries as a result of taking AndroGel: Cribbs, Konrad, and Mitchell suffered myocardial infarctions (heart attacks); Frost suffered a stroke. Plaintiffs Myers, Nolte, and Rowley assert that AndroGel caused them to suffer VTE injuries: Myers and Nolte suffered pulmonary embolisms; Rowley suffered a DVT.

All of the plaintiffs allege injuries that can result from, or are exacerbated by, some form of a clot (thrombus) in the blood. The cardiovascular injures alleged in this case are the result of atherosclerosis, the accumulation of plaque and debris within one or more arteries. Plaque build-up on the arterial walls can result in narrowing of the arteries, limiting blood flow. In addition, in certain circumstances, platelets and red blood cells can adhere to and clump around the plaque, ultimately forming a clot. If the

clot interrupts blood flow through the artery to the heart, a heart attack occurs. If the clot interrupts blood flow to the brain, an ischemic stroke occurs. It is well established and undisputed that certain factors increase one's risk of a heart attack or ischemic stroke, including increased age, smoking, obesity, elevated blood cholesterol level, and high blood pressure.

Like the cardiovascular injures alleged in this litigation, VTE injuries also result from clotting, but in veins rather than arteries. The relevant medical literature recognizes three factors, sometimes referred to as "Virchow's triad," that cause or contribute to the formation of problematic clotting in the veins: (1) slowing or stasis of blood flow in the veins, (2) damage to the blood vessel walls, and (3) hypercoagulability, or abnormal predisposition of the blood to form clots. A deep vein thrombosis (DVT) occurs when blood clots form in a deep vein, usually in the legs, causing pain and swelling. A clot that breaks off and travels to a new part of the body is called an embolus. A pulmonary embolism occurs when an embolus travels to and lodges in a pulmonary blood vessel, blocking blood flow to the lungs. As in the case of the alleged cardiovascular injuries, it is undisputed that there are number of well-established risk factors for VTEs. Established genetic risk factors include a so-called Factor V Leiden mutation, a prothrombin gene mutation, protein C and protein S deficiencies, and antithrombin III deficiency. Established acquired risk factors include prolonged immobilization, previous thromboembolism, recent major surgery, trauma, pregnancy, and polycythemia (elevated volume of red blood cells).

Plaintiffs' experts posit a number of potential mechanisms by which AndroGel and other TRT drugs might increase the risk of cardiovascular and VTE injuries.

Specifically, plaintiffs' experts suggest TRT is pro-thrombotic—that is, it increases the risk of blood clots—because of its tendencies to increase (1) estradiol, a metabolite of testosterone and a form of estrogen, which has been connected to increased risk of clot formation; (2) thromboxane A2 receptors, which can promote abnormal platelet function and increased risk of clotting; and (3) hematocrit (the ratio of the volume of red blood cells to the total volume of blood), which can increase blood viscosity, leading to a higher incidence of clotting.[3] Plaintiffs have retained a number of expert witnesses to testify about these potential biological mechanisms, as well as the medical and scientific literature concerning the possible association between TRT and cardiovascular or VTE injuries. Two cardiologists, Dr. Hossein Ardehali and Dr. Phillip Cuculich, and an epidemiologist, Dr. Burt Gerstman, have prepared expert reports in support of their opinions that TRT increases the risk of heart attacks and strokes. Dr. Henry Rinder, an internal medicine doctor specializing in hematology, has provided expert reports in support of his opinion that TRT increases the risk of VTE injuries. Dr. Perry Halushka, a doctor of internal medicine specializing in pharmacology, offers an opinion primarily regarding the effects of TRT on thromboxane A2 receptor activation, and he concludes that TRT's tendency to increase density of thromboxane A2 receptors can increase the risk of both cardiovascular and VTE injuries. Though each of the aforementioned experts discusses studies regarding the potential association between TRT and the alleged injuries, plaintiffs have also retained a biostatistician, Dr. Martin T. Wells, to offer testimony assessing the statistical power of studies concerning the connection between

[3] Plaintiffs' experts suggest other possible mechanisms by which TRT might increase the risk of cardiovascular injuries in addition to its pro-thrombotic effects, including through TRT's effects on smooth muscle in the arteries, production of reactive oxygen species, and constriction of blood vessels.

TRT and cardiovascular risk. AbbVie offers the testimony of its own expert in statistics, Dr. M. Laurentius Marais, who provides an analysis of the studies relied upon by plaintiffs' experts. (AbbVie has also retained other experts on various issues, but plaintiffs have not challenged the admissibility of their testimony.)

The existing medical literature contains at least thirty peer-reviewed epidemiological studies that assess the potential association between TRT and either cardiovascular events or VTEs. Experts on both sides of this litigation provide extensive analysis of four studies that reported a statistically significant association between TRT and increased cardiovascular events, studies which prompted a petition to the FDA from a public advocacy group and a subsequent investigation of the four studies and the potential risks of TRT. *See* Shehzad Basaria et al., *Adverse Events Associated with Testosterone Administration*, 363 New Eng. J. of Med. 109 (2010) (the Basaria study); Lin Xu et al., *Testosterone Therapy and Cardiovascular Events among Men: A Systematic Review and Meta-Analysis of Placebo-Controlled Randomized Trials*, 11 BMC Med. 108 (2013) (the Xu meta-analysis); Rebecca Vigen et al., *Association of Testosterone Therapy with Mortality, Myocardial Infarction, and Stroke in Men with Low Testosterone Levels*, 310 JAMA 1829 (2013) (the Vigen study); William D. Finkle et al., *Increased Risk of Non-Fatal Myocardial Infarction Following Testosterone Therapy Prescription in Men*, 9 PLOS ONE e85805 (2014) (the Finkle study). Plaintiffs' experts point to these and other studies as evidence that TRT increases users' cardiovascular risks. AbbVie argues that the studies on which plaintiffs' experts rely are flawed and that the majority of the published epidemiology supports AbbVie's position that TRT is not associated with increased cardiovascular risks.

With regard to the connection between TRT and increased risk of VTEs, AbbVie emphasizes four retrospective database studies that have addressed the question, most of which reported no association between TRT and increased VTE risk, and none of which found a statistically significant association between VTE and TRT when considering all groups of TRT users. *See* Jacques Baillargeon et al., *Risk of Venous Thromboembolism in Men Receiving Testosterone Therapy*, 90 Mayo Clinic Proc. 1038 (2015) (the Baillargeon study); Rishi Sharma et al., *Association Between Testosterone Replacement Therapy and the Incidence of DVT and Pulmonary Embolism: A Retrospective Cohort Study of the Veterans Administration Database*, 150 Chest 563 (2016) (the Sharma study); Hu Li et al., *Association between Use of Exogenous Testosterone Therapy and Risk of Venous Thrombotic Events among Exogenous Testosterone Treated and Untreated Men with Hypogonadism*, 195 J. Urology 1065 (2016) (the Li study); Carlos Martinez et al., *Testosterone Treatment and Risk of Venous Thromboembolism: Population Based Case-Control Study*, 355 BMJ i5968 (2016) (the Martinez study). Despite the findings of these studies, plaintiffs and their expert Dr. Rinder maintain that TRT and VTEs are associated. Dr. Rinder contends that the retrospective database studies regarding TRT and VTEs are seriously flawed, and he places greater emphasis on case series and other clinical data in forming his opinion in this case.

AbbVie disputes the contention of plaintiffs and their experts that the medical and scientific literature supports an association between TRT and plaintiffs' alleged injuries. According to AbbVie, not only does the relevant scientific literature fail to show that TRT increases the risk of cardiovascular or VTE injuries, but the most recent observational

study suggests that TRT has a *protective* effect against cardiovascular injury. *See* T. Craig Cheetham et al., *Association of Testosterone Replacement with Cardiovascular Outcomes among Men with Androgen Deficiency*, 177 JAMA Intern. Med. 491 (2017) (the Cheetham study). AbbVie contends that plaintiffs' experts lack a scientific basis, in the published literature or elsewhere, for their opinions that TRT is capable of causing the alleged injuries and argues that their opinions are therefore unreliable and must be excluded. Plaintiffs, for their part, have moved to exclude or limit the testimony of Dr. Marais, largely on the basis that his lack of expertise in medicine and biology renders him unqualified to opine on epidemiology and biostatistics.

In arguing that the scientific literature does not support a finding that TRT is associated with the alleged injuries, AbbVie emphasize the importance of considering the statistical significance of study results. Though experts for both AbbVie and plaintiffs agree that statistical significance is a widely accepted concept in the field of statistics and that there is a conventional method for determining the statistical significance of a study's findings, the parties and their experts disagree about the conclusions one may permissibly draw from a study result that is deemed to possess or lack statistical significance according to conventional methods of making that determination.

Statisticians test for statistical significance to determine the likelihood that a study's findings are due to chance. Take, for example, a study examining whether smoking cigarettes increases one's risk for developing a particular disease. Statisticians often express the result of such a study in terms of an odds ratio (sometimes expressed as "relative risk" where the outcome measured is rare and the

odds ratio provides a reasonable approximation of the relative risk). If the incidence of developing the disease is the same for both smokers (the treatment group) and non-smokers (the control group), the ratio will be 1.0. A positive ratio, such as 1.5, would indicate a higher incidence of the disease among smokers. According to conventional statistical practice, such a result—that is, a finding of a positive association between smoking and development of the disease—would be considered statistically significant if there is a 95% probability, also expressed as a "p-value" of <0.05, that the observed association is not the product of chance. If, however, the p-value were greater than 0.05, the observed association would not be regarded as statistically significant, according to prevailing conventions, because there is a greater than 5% probability that the association observed was the result of chance.

Statistical significance can also be expressed equivalently in terms of a confidence interval. A confidence interval consists of a range of values. For a 95% confidence interval, one would expect future studies sampling the same population to produce values within the range 95% of the time. So if the confidence interval ranged from 1.2 to 3.0, the association would be considered statistically significant, because one would expect, with 95% confidence, that future studies would report a ratio above 1.0—indeed, above 1.2. If, however, the confidence interval range includes values below 1.0—for example, from 0.5 to 3.0—the observed association would not be statistically significant, because one could not say with confidence that the association would be observed in a future study.

According to AbbVie, to establish that AndroGel is capable of causing plaintiffs' alleged injuries, plaintiffs' experts must point to literature establishing a statistically

significant association between TRT and the alleged injuries—that is, with odds ratios above one and with p-values below 0.05 (or 95% confidence intervals that do not include 1.0 within their range). Plaintiffs and their experts argue that AbbVie overemphasizes the importance of conventional determinations of statistical significance. They contend that a study reporting a confidence interval ranging from 0.9 to 3.5, for example, should certainly not be understood as evidence that there is *no association* and may actually be understood as evidence in favor of an association, when considered in light of other evidence. Thus, according to plaintiffs' experts, even studies that do not show a statistically significant association between TRT and the alleged injuries may plausibly bolster their opinions that TRT is capable of causing such injuries.

Plaintiffs also intend to offer expert testimony regarding specific causation—that is, whether AndroGel was the cause of each plaintiff's alleged injury. In addition to their opinions regarding general causation, Drs. Ardehali and Cuculich opine, respectively, that AndroGel use was the cause of the heart attacks suffered by Mitchell and Konrad. Dr. John Setaro, a cardiologist, incorporates the general causation opinions of Drs. Ardehali and Rinder in reaching his conclusion that AndroGel use was the cause of Cribbs's heart attack. Dr. Ronald Ziman, a doctor in internal medicine specializing in vascular neurology, also incorporates the general causation opinions of Drs. Ardehali and Rinder in forming his expert opinion that AndroGel was the cause of Frost's stroke. Dr. Rinder provides specific-causation expert reports for Myers, Nolte, and Rowley, opining that AndroGel use was the cause of their VTE injuries. Each of plaintiffs' specific-causation experts purports to employ a "differential diagnosis" or "differential

etiology" to reach his conclusion. When using that methodology, an expert "rules in all the potential causes of a patient's ailment and then by systematically ruling out causes that would not apply to the patient, the physician arrives at what is the likely cause of the ailment." *Myers v. Ill. Cent. R.R. Co.*, 629 F.3d 639, 644 (7th Cir. 2010). Although "[t]here is nothing controversial about that methodology," *id.*, AbbVie argues that none of plaintiffs' experts appropriately apply the method, rendering their opinions unreliable and inadmissible.

Because causation is a required element of all of plaintiffs' claims, AbbVie argues, the lack of admissible expert testimony regarding general and specific causation requires the Court to grant summary judgment in each bellwether case. Plaintiffs maintain that their proposed experts have provided reliable, scientific bases for their opinions, such that their testimony should be allowed and AbbVie's motion for summary judgment denied. The Court addresses the parties' arguments below, first considering plaintiffs' challenge to Dr. Marais' testimony before analyzing the opinions of plaintiffs' experts regarding general and specific causation.

Discussion

A. Legal standards for testimony by an expert witness

Federal Rule of Evidence 702 governs the admissibility of expert testimony. It provides:

> A witness who is qualified as an expert by knowledge, skill, experience, training, or education may testify in the form of an opinion or otherwise if:
>
> (a) the expert's scientific, technical, or other specialized knowledge will help the trier of fact to understand the evidence or to determine a fact in issue;
>
> (b) the testimony is based on sufficient facts or data;

(c) the testimony is the product of reliable principles and methods; and

(d) the expert has reliably applied the principles and methods to the facts of the case.

Fed. R. Evid. 702. Under *Daubert*, the district court plays the role of gatekeeper in determining whether proposed expert testimony meets the standards of Rule 702. *Daubert*, 509 U.S. at 597. The Seventh Circuit[4] has described the district court's gatekeeping role as having three steps: determining (1) whether the witness is qualified, (2) whether the expert's applied methodology is scientifically reliable, and (3) whether the testimony will assist the trier of fact to understand the evidence or determine a fact in issue. *Myers*, 629 F.3d at 644.

A considerable body of case law since *Daubert* provides guidance regarding how a district court should exercise its gatekeeping role. To determine whether an expert is sufficiently qualified, a court should consider the expert's "full range of practical experience as well as academic or technical training." *Smith v. Ford Motor Co.*, 215 F.3d 713, 718 (7th Cir. 2000) (hereinafter "*Ford Motor Co.*"). Regarding an expert's qualifications, the question "is not whether an expert witness is qualified in general, but whether his qualifications provide a foundation for him to answer [the] specific question" he purports to answer. *Gayton v. McCoy*, 593 F.3d 610, 617 (7th Cir. 2010). In determining the reliability of an expert's opinion, "[t]he focus . . . must be solely on principles and methodology, not on the conclusions that they generate." *Daubert*, 509

[4] When applying federal law, such as the law regarding admissibility of evidence in federal court, the transferee court in an MDL proceeding applies the law of the circuit in which it sits. *See, e.g.*, *In re Zimmer Nexgen Knee Implant Prod. Liab. Litig.*, No. 11 C 5468, 2012 WL 3582708, at *5 (N.D. Ill. Aug. 16, 2012).

U.S. at 595. "The soundness of the factual underpinnings of the expert's analysis and the correctness of the expert's conclusions based on that analysis are factual matters to be determined by the [jury]." *Ford Motor Co.*, 215 F.3d at 718. An expert, however, must provide some reliable basis for the conclusions he reaches. A court may properly exclude "opinion evidence that is connected to existing data only by the *ipse dixit* of the expert." *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997). To offer a reliable opinion, an expert must "employ[] in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 152 (1999). Relevant factors for assessing the reliability of an expert's methods include "(1) whether the scientific theory or technique can be (and has been) tested; (2) whether the theory or technique has been subjected to peer review and publication; (3) whether a particular technique has a known potential rate of error; and (4) whether the theory or technique is generally accepted in the relevant scientific community." *Schultz v. Akzo Nobel Paints, LLC*, 721 F.3d 426, 431 (7th Cir. 2013). But "[i]mportantly, this list is neither exhaustive nor mandatory." *C.W. ex rel. Wood v. Textron, Inc.*, 807 F.3d 827, 835 (7th Cir. 2015). A court should ultimately determine reliability on a case-by-case basis. *Id.* Finally, in addition to being reliable, the expert's testimony must assist the trier of fact. In other words, it must "fit" the facts of the case and have "a valid scientific connection to the pertinent inquiry." *Daubert*, 509 U.S. at 591–92.

The proponent of expert testimony bears the burden of establishing, by a preponderance of the evidence, that the testimony satisfies *Daubert*'s standards and is otherwise admissible under the Rules of Evidence. *Lewis v. CITGO Petroleum Corp.*,

561 F.3d 698, 705 (7th Cir. 2009). When determining whether the proponent of expert testimony has met that burden, however, a court must be mindful that "[a] *Daubert* inquiry is not designed to have the district judge take the place of the jury to decide ultimate issues of credibility and accuracy." *Lapsley v. Xtek, Inc.*, 689 F.3d 802, 805 (7th Cir. 2012). If the credibility or accuracy of an expert opinion is in question, the proper remedy is not exclusion of the testimony, but rather testing the opinion before the jury using the traditional tools of "[v]igorous cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof." *Daubert*, 509 U.S. at 596.

B. Dr. Marais' testimony

Plaintiffs' motion to limit Dr. Marais' testimony is based almost entirely on their contention that Dr. Marais is unqualified to offer many of the opinions expressed in his expert report.[5] Dr. Marais is vice president of a consulting firm that specializes in applied mathematical and statistical analyses. He holds a Ph.D. in business administration and mathematics, as well as master's degrees in statistics and mathematics, all from Stanford University. He has taught and conducted research while on the faculties of the University of Chicago and Stanford, and he is a member of a number of professional societies related to mathematics and statistics.

Given Dr. Marais' background, plaintiffs do not dispute that Dr. Marais is qualified in general to offer expert opinions on statistical and mathematical matters. They do

[5] Plaintiffs also assert that Dr. Marais did not use a recognized methodology in rendering his opinions and that his opinion will confuse, rather than assist, the jury. Plaintiffs provide no analysis or support for those arguments, however, and thus the Court need not and does not address them. *See Crespo v. Colvin*, 824 F.3d 667, 674 (7th Cir. 2016) ("[P]erfunctory and undeveloped arguments, and arguments that are unsupported by pertinent authority, are waived.").

argue, however, that the statistical analysis at issue in this case, and the statistical opinions Dr. Marais intends to offer, concern specific sub-fields of statistics—biostatistics and epidemiology—in which he lacks expertise. According to plaintiffs, proper statistical analysis of biological or medical studies involves the exercise of medical and scientific judgment based on training and experience in medicine, biology, or a related field. Because Dr. Marais has no experience and training in such a field, plaintiffs argue, he is unqualified to offer many of his proposed opinions in this case.

The Court agrees with plaintiffs in general that the practice of biostatistics and epidemiology often requires medical or other specific scientific expertise. But the Court is not persuaded that Dr. Marais lacks the necessary expertise to render the particular opinions he intends to offer in this case. As the Seventh Circuit has made clear, the inquiry into an expert's qualifications is not a generalized one: rather, a court "must look at each of the conclusions [the expert] draws individually to see if he has the adequate education, skill, and training to reach them." *Gayton*, 593 F.3d at 617. In support of their motion to limit his testimony, plaintiffs do address Dr. Marais' conclusions individually, explaining why they believe he is unqualified to offer them, but each conclusion plaintiffs challenge lies within the scope of his expertise as a statistician.

First, plaintiffs argue that Dr. Marais is unqualified to offer an opinion about the effect of excluding certain cardiovascular adverse events from the Basaria study. Dr. Marais lacks the medical expertise, plaintiffs argue, to determine the appropriateness of excluding those events from the study. But Dr. Marais explained during his deposition that it was Dr. William J. French, another of AbbVie's experts, who suggested that Dr. Marais focus on major adverse cardiac events as opposed to all of the adverse

cardiovascular events included in the Basaria study. It is undisputed that Dr. French, a cardiologist, is qualified to make a judgment about which cardiovascular events are most relevant to this case, and thus it was appropriate for Dr. Marais to follow his suggestion. And Dr. Marais is qualified to assess the statistical effect of removing such events from the Basaria study's underlying data.

Second, plaintiffs object to Dr. Marais' critique of the Xu meta-analysis. Dr. Marais performed a statistical "sensitivity analysis" to determine the extent to which the results of the Basaria study drove the results of the Xu meta-analysis. Plaintiffs argue that Dr. Marais' critique of the Xu meta-analysis is inadmissible because it rests on his purportedly inadmissible analysis of the Basaria study. As just discussed, Dr. Marais is qualified to analyze the Basaria study in the way he did, and thus his analysis of the Xu meta-analysis is also appropriate. In addition, the "sensitivity analysis" that Dr. Marais conducted involves the application of a statistical method that is well within the scope of his statistical expertise and does not require any biological or medical background.

Third, plaintiffs argue that Dr. Marais is unqualified to criticize the Vigen study for using a novel statistical method. As a statistical expert, however, Dr. Marais is obviously qualified to assess the appropriateness of the statistical method used in a study. Plaintiffs note that one of AbbVie's own experts in epidemiology refrained from opining on the Vigen study during his deposition because he is not a biostatistician, but a review of that expert's deposition makes clear that it was his lack of *statistical* expertise that kept him from commenting on the study, not his lack of other scientific knowledge. Dr. Marais possesses the requisite statistical expertise to opine about the statistical methods used in the Vigen study.

Fourth, plaintiffs maintain that Dr. Marais is unqualified to criticize the Finkle study for lacking a control group and for failing to control for potential biases. But the importance of a control group and the need to control for bias are central statistical concepts about which Dr. Marais is certainly qualified to testify, and plaintiffs have failed to suggest how Dr. Marais' discussion of these concepts ventures into territory outside his expertise.

Plaintiffs challenge Dr. Marais' qualifications to offer opinions on a number of other subjects. They contend that he is unqualified to opine about the findings of various government investigations into the risks of TRT, but in offering that opinion, Dr. Marais states carefully that he only agrees with the findings of those investigations to the extent their conclusions rest on statistical matters. Such statistical matters are, of course, within his expertise as a statistician. In addition, plaintiffs take issue with Dr. Marais' criticism of certain data adjustments plaintiffs' expert Dr. Gerstman made in conducting his own meta-analysis[6] of studies. But a review of this section of Dr. Marais' export report makes clear that Dr. Marais' criticisms of Dr. Gerstman's methods are statistical in nature and do not rest on biological or medical judgment. Plaintiffs also object to Dr. Marais' opinion that their theory of elevation of cardiovascular risk for transdermal TRT lacks coherence, because, according to plaintiffs, "coherence" is an epidemiological term, an assessment of which requires expertise in epidemiology. Dr. Marais testified, however, that he was not using the word "coherence" as an epidemiological term of art. Rather, he was commenting on the opinion of plaintiffs' expert, Dr. Wells, who reported that there was a greater association between major

[6] A meta-analysis is a statistical procedure for combining data from multiple independent studies.

cardiovascular events for transdermal formulations of TRT as compared to injectable formulations of TRT. According to Dr. Marais, this opinion appears to be inconsistent with (that is, lacking "coherence" with) plaintiffs' position that higher levels of testosterone in the blood (and thus higher levels of estradiol and hematocrit) increases the risk of cardiovascular injuries, because intramuscular TRT has been associated with higher levels of testosterone, estradiol, and hematocrit in the blood than transdermal formulations. Though this opinion of Dr. Marais' arguably requires some biological judgment, the judgment—that an opinion based on greater risk from transdermal TRT is inconsistent with studies suggesting a greater risk from injectable TRTs, based on plaintiffs' theory—is ultimately based more on logic than on biological or medical knowledge. Dr. Marais is free to use that logical point to inform his statistical analysis. To the extent plaintiffs disagree with his biological judgment, they can challenge his assumptions on cross-examination.

Plaintiffs challenge two of Dr. Marais' conclusions concerning causation because, they argue, opinions about causation require the exercise of medical judgment beyond the mere analysis of statistics. The Court agrees with plaintiffs that an opinion about medical or scientific causation often requires going beyond an analysis of statistics to assess, for example, the plausibility of the mechanism by which a purported injury was caused. But because the finding of statistical association is often a prerequisite for a finding of causation, an expert may plausibly conclude that causation is *lacking* merely on the basis of a statistical analysis. And indeed, Dr. Marais' causation opinions do not rely upon specialized scientific or medical judgment. Rather, they are based on his opinion that TRT is not statistically associated with plaintiffs' alleged injuries and his

conclusion that TRT is, *a fortiori*, not a cause of those injuries. He is qualified to opine about a lack of statistical association, and his causation opinion thus follows as a matter of logic.

Plaintiffs also argue that Dr. Marais should not be allowed to offer two opinions about the statistical significance, or lack thereof, of certain associations: namely, his opinions (1) that TRT is associated with a broad range of benefits endpoints and (2) that there is no statistically reliable basis to conclude that elevated estradiol is associated with increased cardiovascular risk. But in reaching his conclusion about the association between TRT and benefits endpoints, Dr. Marais is merely reporting the outcomes of various studies, the authors of which defined certain benefits endpoints and found a statistically significant association between TRT and those endpoints. Dr. Marais is clearly qualified to relay the findings of these authors and confirm that their findings are statistically significant. And with respect to the purported association between elevated estradiol levels and cardiovascular risk, Dr. Marais uses statistical analysis that is well within the scope of his expertise to reach his conclusion that there is no basis for finding an association between estradiol and cardiovascular risk.

In addition to questioning Dr. Marais' qualifications to offer the specific opinions offered in his general expert report, plaintiffs object that Dr. Marais is unqualified to conduct the meta-analysis of certain subgroups of TRT users contained in his report. According to plaintiffs, a comprehensive meta-analysis usually requires, among other things, a qualitative review of the literature in the relevant field and the exercise of biological or other specific scientific judgment to determine which studies should be included and excluded and to interpret the statistical findings in light of other scientific

knowledge. But even if plaintiffs are correct about the scientific knowledge typically required to conduct a meta-analysis, they have not shown how any lack of knowledge or expertise on Dr. Marais' part hindered the particular meta-analysis he conducted for this case. Indeed, Dr. Marais testified that he collaborated with Dr. French in conducting his meta-analysis, and plaintiffs have not disputed that Dr. French possesses the expertise necessary to properly inform Dr. Marais' analysis. To the extent plaintiffs believe Dr. Marais' lack of experience or knowledge led him to include or exclude the wrong data or to draw improper conclusions from his analysis, they will be free to raise those points at trial.

Finally, plaintiffs argue that Dr. Marais is unqualified to offer certain opinions contained in his supplemental report, which he submitted after plaintiff's initial motion to limit his testimony. Some of the opinions plaintiffs identify in the supplemental report do at first glance appear to involve scientific or medical judgment based on specific knowledge. But to the extent they do, Dr. Marais is upfront about the assumptions he is making in offering those opinions, which are otherwise statistical in nature. *See, e.g.*, Marais Supp. Rep. [dkt. no. 1855-1] at ¶ 13 ("I understand that atherosclerosis is a progressive disease; thus, including age as a *binary* covariate likely fails to capture adequately the effect of age.") (emphasis in original). Should plaintiffs or their experts disagree with the assumptions Dr. Marais makes in reaching his statistical conclusions, they will be able to press Dr. Marais on those points during cross-examination at trial.

C. Plaintiffs' experts' testimony regarding causation

Though federal law supplies the standards by which the Court evaluates the admissibility of expert testimony, the law of the states from which plaintiffs' cases

originated governs the substance of plaintiffs' state-law claims. *See, e.g.*, *In re Watson Fentanyl Patch Prod. Liab. Litig.*, 977 F. Supp. 2d 885, 888 (N.D. Ill. 2013) (Kennelly, J.). The parties are in agreement that the substantive law of the following states applies, respectively, to plaintiffs' claims: North Carolina (Cribbs), California (Frost), Tennessee (Konrad), Oregon (Mitchell), Arizona (Myers and Nolte), and Utah (Rowley). The parties also do not dispute that the appropriate test in those states for determining causation in products liability claims is whether the product at issue was a "substantial factor" in bringing about the plaintiff's injury. The Court makes note of this standard at the outset of its discussion of plaintiffs' experts' proposed testimony because the Seventh Circuit has indicated that a district court should consider the relevant substantive causation standard when assessing the reliability of expert testimony regarding causation. *See Schultz*, 721 F.3d at 433 (noting "substantial factor" standard applied under governing state law in assessing whether expert's failure to rule out potential causes of injury rendered causation opinion unreliable). There is also no dispute that plaintiffs' claims require proof of both general and specific causation. As the Seventh Circuit has explained, general causation concerns whether the product or substance at issue had the capacity to cause the injury alleged, and specific causation deals with whether the product or substance was, in fact, the cause of alleged injury. *Wood*, 807 F.3d at 831. The Court discusses plaintiffs' expert testimony regarding general causation of cardiovascular injuries and VTE injuries before addressing the proposed testimony regarding specific causation.

1. General causation of cardiovascular injuries

a. Methodology for establishing general causation

AbbVie does not challenge the qualifications of plaintiffs' causation experts. Instead, it focuses its attack on the reliability of the methodologies the experts use in reaching their opinions that TRT is capable of causing plaintiffs' alleged injuries. The Court focuses in this section on the challenges to the testimony of plaintiffs' experts concerning cardiovascular injuries.

According to AbbVie, plaintiffs' experts fail to employ established methodology for determining causation in a pharmaceutical products liability case. That method, on AbbVie's account, requires the expert to first establish the existence of an association between the drug at issue and the alleged injury, based on epidemiological studies showing an association that is statistically significant. Once such an association is established, AbbVie contends, an expert must next determine whether the relationship between the drug and the injury satisfy other causal criteria, such as the so-called Bradford Hill criteria. *See* A.B. Hill, *The Environment and Disease: Association or Causation?*, 58 Proc. Royal Soc'y Med. 295 (1965) (*Hill*) (listing nine guidelines to consider in determining whether a causal relationship exists). These criteria include the consistency and strength of the relationship, the temporal relationship between exposure and injury, the dose-response relationship (whether increased dosage leads to increased risk), whether the findings of association have been replicated, biological plausibility of causal mechanisms, coherence between epidemiology and laboratory findings, specificity of the association between exposure and effect, and analogy (effect of similar drugs). According to AbbVie, the general-causation opinions of plaintiffs'

cardiovascular experts are unreliable as an initial matter because they have not demonstrated that there is a statistically significant association between TRT and increased cardiovascular risk. But even if such an association did exist, AbbVie argues, the experts' opinions would still be unreliable because they have failed to show that the other well-accepted causal criteria have been satisfied.

Plaintiffs dispute that a valid opinion regarding causation must involve a finding of a statistically significant association in the epidemiological literature followed by a checklist analysis of the Bradford Hill factors or other causal criteria. Rather, plaintiffs argue, an expert is permitted to form an opinion based on the "totality of the evidence," which may include analysis of randomized control trials, observational studies, meta-analyses, case reports, and animal and *in vitro* studies, as well as criteria such as the plausibility of proposed causal mechanisms, the magnitude of reported findings of association, and results of studies in analogous circumstances. The Court agrees with plaintiffs that there is nothing inherently unreliable about a method that relies on the totality of the evidence, provided that the expert considers the evidence carefully and explains how the weight of the various pieces of evidence led him to his conclusion. Mere "expert intuition," of course, is not a reliable methodology.[7] *Zenith Elecs. Corp. v. WH-TV Broad. Corp.*, 395 F.3d 416, 419 (7th Cir. 2005). But an expert may rely upon a method according to which "each body of evidence [is] treated as grounds for the

[7] AbbVie specifically criticizes Dr. Gerstman for relying on what he calls a "gestalt" approach to drawing a conclusion from the available evidence. Though the term "gestalt" may suggest an intuitive or "gut" approach to assessing evidence, which would be unreliable, Dr. Gerstman's testimony makes clear that by using the term "gestalt," he is referring to an approach by which one attempt to "consistent[ly] combin[e] all the sources of information." Gerstman Dep. [dkt. no. 1813-3] 360:19–21. That approach is consistent with the totality-of-the-evidence method, and Dr. Gerstman's use of the word "gestalt" is not a basis for excluding his testimony.

subsidiary conclusion that it would, if combined with other evidence, support a causal inference." *Milward v. Acuity Specialty Prod. Grp., Inc.*, 639 F.3d 11, 23 (1st Cir. 2011); *see also id.* ("The hallmark of the weight of the evidence approach is reasoning to the best explanation for all of the available evidence.").

As part of their consideration of the totality of the evidence, plaintiffs' experts conclude that the scientific literature supports a finding that TRT is associated with increased cardiovascular risk. That opinion is based to some extent on the results of studies that *do* show a statistically significant association between TRT and elevated cardiovascular risk among certain populations. The Basaria study, for example, reported a statistically significant odds ratio of 5.4 for increased cardiovascular risk among the population it studied (men over the age of 65 with mobility limitations). Regarding other subpopulations, the Finkle study reported statistically significant associations between TRT and increased cardiovascular risk for users over the age of 65 (odds ratio of 2.2) and in men under 65 with preexisting heart disease (odds ratio of 2.9). Other studies, including a meta-analysis, have found statistically significant increases among short-term users of all ages. *See, e.g.*, Stewart G. Albert & John E. Morley, *Testosterone Therapy, Association with Age, Initiation and Mode of Therapy with Cardiovascular Events: A Systematic Review*, 85 Clinical Endocrinology 436 (2016) (the Albert meta-analysis).[8]

AbbVie and its experts point out a number of purported flaws in such studies and

[8] When the authors of the Albert meta-analysis analyzed subgroups of short-term users, the statistically significant association did not persist for users under 65 years old. The Xu meta-analysis, which reviewed less data than the later Albert meta-analysis, did find a statistically significant association among all users.

argue that no study in the epidemiological literature supports a conclusion that TRT is associated with increased cardiovascular risk in the population of users as a whole, especially because numerous epidemiological studies have found no association at all. Plaintiffs' experts, however, consider and address the purported flaws of the studies on which they rely and also offer their own criticisms of the studies that have not found any association between TRT and increased cardiovascular risk. Dr. Wells, for example, conducts an analysis of the statistical power[9] of two meta-analyses (including the Albert meta-analysis) that found no such overall association. According to Dr. Wells' analysis, those studies were so underpowered, based on factors like the size of the sample studied, that they would be unlikely to detect an association even if one were present. Thus, according to Dr. Wells, the risk of a Type II error (a false negative, or mistaken finding of no effect) in those studies was unacceptably high. On the other hand, he explains that the size of the effect in a study like Basaria is so significant that even though that study was underpowered, the risk of a Type I error (false positive) is low. In addition to lack of power, plaintiffs point to other problems in the studies that appear to favor AbbVie's position, including various biases and purported flaws specific to the individual studies. Plaintiffs' experts note, for example, that findings of association among short-term users but not among long-term users are more likely the product of the study design (failure to protect against survivor bias, for example) than a result of the actual effects of short-term versus long-term use. As another example of a purported flaw in the studies on which AbbVie relies, plaintiffs point to the Xu meta-analysis, which separately analyzed industry-fund studies and non-industry-funded

[9] "Statistical power" refers to the likelihood that a study will detect an effect when there is an effect to be detected.

studies. The analysis and found a 2.06:1 ratio for the non-industry-funded studies, as compared to a 0.89:1 ratio for the industry-funded studies, suggesting the possibility of publication bias.

To support their opinion that the scientific literature supports an association between TRT and increased cardiovascular risk for the population of users at large, plaintiffs' experts also push back against AbbVie's and its experts' rigid reliance on the concept of statistical significance. As Dr. Wells explains, a finding of an association that is not statistically significant does not mean that no association exists. Rather, it is quite possible that the study was underpowered and was thus likely to produce false negatives. Plaintiffs' other experts go further and argue against treating study results with p-values of less than 0.05 as the only results worth considering. They contend that such studies should be considered as part of the totality of the evidence and that studies reporting an association that is not significant to a p-value of less than 0.05 may still be probative of the existence of an association in light of other information. This approach, even if it is not the majority approach among statisticians, appears to be sufficiently accepted among scientific authorities to constitute a reliable method of conducting statistical analysis. *See, e.g.*, Fed. Judicial Ctr., Nat'l Research Counsel of the Nat'l Acads., *Reference Manual on Scientific Evidence* (3d ed. 2011) (RMSE) at 578–79 (discussing controversy regarding appropriate role of significance testing and nothing that "[e]pidemiologists have become increasingly sophisticated in addressing the issue of random error and examining the data from a study to ascertain what information they may provide about [a relationship] without the necessity of rejecting all studies that are not statistically significant").

In addition, this Court and others have concluded previously that epidemiology showing a statistically significant association is not an absolute requirement for a reliable causation opinion, especially in a case where it would be difficult to perform an adequately powered epidemiological study to yield statistically significant evidence of association. *See, e.g.*, *Milward*, 639 F.3d at 24–25 (noting difficulty of performing high-powered study in context of case and concluding that district court erred in ruling that expert's reliance on data that lack statistical significance was a deviation from sound practice of the scientific method); *Smith v. I-Flow Corp.,* No. 09 C 3908, 2011 WL 12556366, at *3 (N.D. Ill. May 3, 2011) (Kennelly, J.) ("There is no rule that requires an expert to base his causation opinion on an epidemiological study."). Because an epidemiological study reporting a statistically signification association is not a prerequisite for a reliable causation opinion, the Court also concludes that it is not necessary, contrary to AbbVie's contention, for plaintiffs' experts to rely on a study whose author herself concludes that a causal connection exists, as long as the experts adequately explain why their view of the evidence supports a finding of causation.

Ultimately, experts on both sides of this litigation have analyzed the existing epidemiological evidence in detail, criticizing the studies on which the other side relies, and drawing different conclusions from the literature. This is not a case in which plaintiffs' experts have simply cherry-picked the favorable studies while ignoring unfavorable studies entirely. *Cf. In re Zoloft (Sertraline Hydrochloride) Prod. Liab. Litig.*, 26 F. Supp. 3d 449, 460–61 (E.D. Pa. 2014) (excluding expert who failed to provide an adequate rationale for excluding her own, unfavorable peer-reviewed studies from her expert report); *In re Rezulin Prod. Liab. Litig.*, 369 F. Supp. 2d 398, 425–26 (S.D.N.Y.

2005) (excluding experts whose reports failed to even mention highly relevant, but unfavorable, studies). At this stage, it is not the Court's role to choose between competing studies. *Schultz*, 721 F.3d at 433. The studies' "merits and demerits . . . can be explored at trial." *Id.*

The Court likewise is not convinced that a causation opinion based on the totality of the evidence must address each Bradford Hill factor. "Although the drawing of causal inferences is informed by scientific expertise, it is not a determination that is made by using an objective or algorithmic methodology." RMSE at 600. In evaluating the totality of the evidence, plaintiffs' experts necessarily considered a number of the Bradford Hill factors, including temporality, the strength and consistency of the purported association, and the plausibility of the biological mechanism by which TRT could cause cardiovascular injuries. That is a sufficient basis for forming an opinion concerning causation. *See Cook v. Rockwell Int'l Corp.*, 580 F. Supp. 2d 1071, 1098 (D. Colo. 2006) (noting lack of authority, "scientific or legal," for proposition "that compliance with all, or even one, of [the Bradford Hill] factors is required for [causation expert's] methodology and conclusions to be deemed sufficiently reliable to be admissible").

Plaintiffs' experts discuss the plausibility of the biological mechanism in particularly extensive detail, relying on various studies and their own biological knowledge to explain how elevated estradiol, thromboxane, and hematocrit, among other mechanisms, may increase cardiovascular risk. AbbVie's primary criticism of plaintiffs' experts' mechanism theories is that the experts do not rely on any studies that demonstrate a link between use of TRT in human beings and the proposed mechanism plus a link between the proposed mechanism to cardiovascular events. But AbbVie

cites to no authority that says experts must be held to so high a standard in demonstrating the plausibility of mechanism. Rather, an analysis of biological plausibility "asks whether the hypothesized causal link is credible in light of what is known from science and medicine about the human body and the potentially offending agent." *Milward*, 639 F.3d at 26. It is sufficient for plaintiffs' experts to provide independent valid bases for determining that the link between TRT and the proposed mechanism is credible and that the proposed mechanism is also credibly linked to the alleged injury. The Court addresses below the issue of what types of studies are permissible in considering biological plausibility.

AbbVie also points to other purportedly unreliable aspects of the methods plaintiffs' experts employ. AbbVie takes issue, for example, with Dr. Gerstman's use of Bayesian statistical methods to analyze epidemiological literature in a supplement to his initial expert report. This portion of Dr. Gerstman's proposed testimony should be excluded, AbbVie argues, because Dr. Gerstman lacks expertise in Bayesian analysis, he continues to use traditional significance testing in his own publications, and the Bayesian approach itself is inappropriately based on subjective assumptions. AbbVie also criticizes his use of Bayesian methods to reach the conclusion that there is an 85% chance that TRT is associated with cardiovascular risk because Dr. Gerstman cannot quantify the size of that risk using Bayesian methods and because his approach would not be considered significant to a 95% confidence level. Despite AbbVie's criticisms, the Court declines to exclude Dr. Gerstman's Bayesian analysis. AbbVie, itself, cites the RMSE's statement that Bayesians are "a well-established minority" in the field of statistics. RMSE at 529; *see Lust By & Through Lust v. Merrell Dow Pharm., Inc.*, 89

F.3d 594, 597 (9th Cir. 1996) (discussing need to show that expert follow method practiced by "(at least) a recognized minority of scientists in his field"). And though Dr. Gerstman has not published a journal article on Bayesian analysis, he is a qualified expert in statistics and discusses Bayesian risk calculations in his epidemiology textbook.

In addition, AbbVie's assertion that Bayesian methods are excessively "subjective" is unsupported; AbbVie does not explain how the subjective aspect of Bayesian analysis renders the method any less reliable than frequentist approaches to statistics, which also involve subjective judgments in interpretation of study results. Regarding Dr. Gerstman's inability to quantify the cardiovascular risk he finds in his Bayesian analysis, that is an issue affecting the weight to be accorded to his analysis, not its admissibility. Finally, AbbVie's criticism of Dr. Gerstman's failure to report a result within a 95% confidence interval appears to be a misapplication of a tool from frequentist statistics to criticize a Bayesian analysis. *See* R.D. Morey et al., *The Fallacy of Placing Confidence in Confidence Intervals*, 23 Psychonomic Bull. & Rev. 103, 119 (2016) ("One of the misconceptions regarding the relationship between Bayesian inference and frequentist inference is that they will lead to the same inferences, and hence all confidence intervals can simply be interpreted in a Bayesian way.").

AbbVie also faults Drs. Gerstman and Ardehali for improperly relying on a risk / benefit analysis and analysis of adverse event reports, respectively, in forming their causation opinions. Plaintiffs respond, however, that neither expert intends to testify about risk / benefit analysis or adverse event reports in support of an opinion regarding causation. Risk / benefit analysis does not appear in any of Dr. Gerstman's expert

reports and was only discussed during his deposition in response to questions from AbbVie's counsel, and he did not indicate that a risk / benefit analysis was the basis for his causation opinions. Similarly, plaintiffs represent that Dr. Ardehali's review of adverse event reports did not inform his causation opinion and is relevant only for his opinion about what AbbVie would or should have learned from the reports.

b. Application of the methodology

In addition to using methods and principles that are reliable, an expert must also "reliably appl[y] the principles and methods to the facts of the case." Fed. R. Evid. 702(d). As discussed above, the Court concludes that plaintiffs' experts' "totality of the evidence" approach is a reliable one, in part, because of how they have applied it. They have not, for example, cherry-picked studies or failed to grapple with contrary evidence. AbbVie suggests that in attempting to address that contrary evidence, plaintiffs' have effectively "proved too much" and undermined the support for their own conclusions. Specifically, AbbVie argues the opinions of Drs. Ardehali, Cuculich, Wells, and Gerstman should be excluded because their criticisms of the epidemiological literature apply to any epidemiological study that favors their position, leaving them with no reliable epidemiological basis for their theories. But this argument overstates the nature of plaintiffs' experts' criticisms. A close review of the expert reports of Drs. Ardehali, Cuculich, and Gerstman reveals that they addressed each study individually, pointing out the merits and demerits of each, and Dr. Wells[10] expressly addressed the difference

[10] AbbVie argues in a footnote that Dr. Wells' testimony will not assist the trier of fact, and should thus be excluded. His opinion will be unhelpful, AbbVie argues, because what he says is already obvious from the texts of the studies he analyzed: that the Basaria study is statistically significant and that the two meta-analyses he examined are underpowered. The Court disagrees that the conclusion Dr. Wells reaches would

in the likelihood of Type I versus Type II errors in this context, showing how plaintiffs could criticize unfavorable studies while still relying on certain studies that favor their position.

AbbVie also charges that the totality of the evidence on which the experts rely is simply insufficient to support their conclusions. According to AbbVie, plaintiffs' experts rely on only a few facially favorable studies, while ignoring (1) those studies' flaws, (2) the fact that the studies are inconsistent with one another, and (3) the studies' authors' own unwillingness to conclude that they demonstrate a causal association.[11] As discussed above, a review of plaintiffs' experts' reports reveals that they carefully addressed the merits, flaws, and implications of both favorable and unfavorable studies. AbbVie is likely correct that no single piece of evidence the experts rely upon is sufficient to support their causation opinions. But the experts have adequately explained why they have reached their conclusions on the basis of the evidence as a whole. *See Milward*, 639 F.3d at 23. The Court's inquiry at this stage is to determine whether the experts "considered sufficient data to employ the methodology," not whether their consideration of the data led to the correct conclusion. *Stollings v. Ryobi Techs., Inc.*, 725 F.3d 753, 766 (7th Cir. 2013). For an expert conclusion that is subject

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be obvious to the lay juror. Even if it were obvious that the meta-analyses were underpowered and that Basaria was statistically significant, Dr. Wells' analysis of the degree to which the meta-analyses were underpowered and his comparison of the likelihood of Type I and Type II errors will be helpful for the trier of fact.

[11] In its reply, AbbVie also faults plaintiffs' experts for failing to address the results of the Cheetham study, which found that TRT had a protective effect against cardiovascular events. That study was published after plaintiffs' expert submitted their reports and after AbbVie filed its motion for summary judgment. Given these circumstances, the Court does not believe that it would be fair or appropriate to exclude an expert's testimony on this basis.

to doubt, "[i]t is the role of the jury to weigh these sources of doubt." *Id.*

In arguing that plaintiffs' experts lack a sufficient basis for their conclusions, AbbVie emphasizes that the FDA reviewed the same data, specifically the same epidemiological studies, as plaintiffs' experts but reached a different conclusion about whether TRT is associated with cardiovascular injuries. AbbVie, however, has not cited any authority for the proposition that conclusions the FDA makes in its review of available data are legally or scientifically dispositive on the issue of causation. In this context, the FDA's opinion is analogous to the opinion of any other expert in this case. Thus, although the FDA may have a different interpretation of the studies relied upon by plaintiffs' experts, "it is left to the trier of fact, not the reviewing court, to decide how to weigh the competing expert testimony." *Wipf v. Kowalski*, 519 F.3d 380, 385 (7th Cir. 2008).

AbbVie also argues that certain types of studies on which the experts rely are either irrelevant or unreliable. Drs. Ardehali and Cuculich devote portions of their report to a discussion of research on athletes' use of anabolic steroids, and Dr. Gerstman devotes a section of his report to a discussion of hormone therapy safety in women. AbbVie argues that studies about anabolic steroids are irrelevant because they involve another class of drugs that are ingested at considerably higher levels than TRT and are administered to a population that is drastically different from the target population for TRT. Studies of female hormone therapy are similarly irrelevant, AbbVie argues, because they involve an obviously different drug administered to an obviously different population. Studies about anabolic steroids and female hormone therapy would, by themselves, be insufficient data on which to base an expert opinion about TRT. But the

studies are not so disconnected from the facts of this case that they render plaintiffs' experts' opinions unreliable. Evidence that high levels of testosterone in athletes have adverse effects may shed some light on the effects of lower (but still elevated) levels in non-athletes. And the fact that testosterone metabolizes into estradiol makes it reasonable to consider how increased levels of estrogen affected women under hormone therapy. Indeed, such evidence could be particularly relevant for analyzing the plausibility of increased estradiol as a mechanism. As Bradford Hill himself recognized, analogy—or consideration of similar evidence with another drug or disease—may be relevant to a causation analysis. *Hill* at 299.

According to AbbVie, plaintiffs' experts' reliance on animal studies and *in vitro* studies is also inappropriate. Some courts have cautioned against drawing conclusions about causation in human beings on the basis of such studies because of biological differences between animals and human beings and between human tissue and living human beings. *See, e.g.*, *In re Prempro Prod. Liab. Litig.*, 738 F. Supp. 2d 887, 894 (E.D. Ark. 2010). But as in the case of the anabolic steroid and female hormone studies discussed above, the Court would find the experts' reliance on animal and *in vitro* studies more problematic if those studies provided the only or, perhaps, the primary basis for the experts' causation opinions. Instead, plaintiffs' experts rely on such studies as part of a much broader set of evidence and primarily for the purpose of determining biological plausibility, for which animal studies and *in vitro* studies may be among the most useful available evidence. *See, e.g.*, *In re Actos (Pioglitazone) Prod. Liab. Litig.*, No. 12-CV-00064, 2013 WL 6796461, at *12 (W.D. La. Dec. 19, 2013) (approving of reliance on animal studies to show biological plausibility); *Smith*, 2011 WL 12556366, at

*3 (admitting opinion of expert who relied in part upon *in vitro* studies and animal studies).

AbbVie also argues for the exclusion of one of Dr. Ardehali's opinions because it is not based on any supporting data. Specifically, AbbVie contends that Dr. Ardehali should not be permitted to opine that TRT increases the risk of heart attack and stroke only in TRT users who have non-classical hypogonadism. Plaintiffs do not address this argument in their response. From the Court's own review of Dr. Ardehali's report, it is unclear whether he is offering the opinion AbbVie attributes to him. It appears that Dr. Ardehali may be arguing that an older population is already likely to have particular risk factors that would make TRT especially dangerous for them, and thus he may conclude that because most TRT users with non-classical hypogonadism are older, their cardiovascular risk is greater. Or Dr. Ardehali may be arguing that the benefits of TRT for patients with classical hypogonadism outweigh the increased cardiovascular risks. Dr. Ardehali does appear to have adequate support to assert either of those opinions. If, however, his contention is the one AbbVie suggests—that TRT's increased cardiovascular risk is greater among users with non-classical hypogonadism *because they have non-classical as opposed to classical hypogonadism*—the Court agrees with AbbVie that Dr. Ardehali has not provided support for this opinion and that it is not admissible.

2. General causation of VTE injuries

Like the opinions of plaintiffs' experts on general causation of cardiovascular injuries, the Court concludes, despite challenges from AbbVie, that the opinions of Drs.

Rinder and Halushka[12] concerning general causation of VTE injuries are reliable. As with the cardiovascular experts, Dr. Rinder (plaintiffs' primary VTE expert) reliably applies a "totality of the evidence" method, considering the available epidemiological literature and other clinical data, in addition to exploring the plausibility of the proposed mechanisms by which TRT increases VTE risk. Many of AbbVie's arguments against the admission of Dr. Rinder's testimony are similar to those leveled against plaintiffs' cardiovascular experts. For the same reasons discussed above, the Court rejects AbbVie's challenges to Dr. Rinder's testimony based on his purported failure to cite a statistically significant association in the epidemiological literature or to address all of the Bradford Hill criteria, as well as his reliance on animal studies and female hormone studies.

Regarding epidemiology, Dr. Rinder's opinion differs from those of plaintiffs' cardiovascular experts in an important respect—namely, there is considerably less epidemiological evidence to consider regarding the relationship between TRT and VTEs. As opposed to the more than two dozen studies addressing TRT and cardiovascular risk, there are only four epidemiological studies addressing TRT and VTEs. Of those studies, only the Martinez study found a statistically significant association between VTE and any subgroup of TRT users. The association for users

[12] Dr. Halushka's opinion is focused primarily on one of the proposed mechanisms by which TRT causes plaintiffs' alleged injuries: increased thromboxane A2 receptors. Because this mechanism is proposed for both cardiovascular and VTE injuries, his testimony is relevant to both types of injuries. AbbVie suggests that because Dr. Halushka does not discuss epidemiology in his report, his causation opinion is unreliable. The Court, however, interprets Dr. Halushka's opinion to be focused primarily on one proposed mechanism, allowing him to reach only the limited conclusion that TRT "can" cause cardiovascular and VTE injuries. Such an opinion is reliable even without the consideration of epidemiology.

overall was not statistically significant (confidence interval from 0.94–1.66), though the authors did find a statistically significant association among users who had taken TRT for six months or less (confidence interval from 1.12–2.37) and in other subgroups. The other studies—the Sharma, Li, and Baillargeon studies—found no statistically significant association. AbbVie argues that Dr. Rinder cannot reliably conclude that TRT can cause VTEs without epidemiological evidence showing a statistically significant association. In his report, Dr. Rinder discusses each of the available epidemiological studies and explains why they are flawed. Those purported flaws include publication bias, selection bias in the studies' inclusion and exclusion criteria, and a general problem with the reliability of retrospective studies to assess risks of the kind at issue in this case.

For the most part, although the epidemiology appears to show a stronger connection between TRT and cardiovascular injuries, the Court's reasons for rejecting the necessity of an epidemiological study showing a statistically significant association in the cardiovascular context apply with greater force in the VTE context. It is true that the lack of statistically significant findings of association hurts the strength of Dr. Rinder's analysis, but the dearth of studies researching the question means it less likely that such associations would have been found. Where the existing epidemiological research is limited or nonexistent, courts are more willing to allow expert testimony on causation that does not depend on epidemiological sources. *See, e.g.*, *Smith*, 2011 WL 12556366, at *3 ("There is no rule that requires an expert to base his causation opinion on an epidemiological study."); *Tucker v. SmithKline Beecham Corp.*, 701 F. Supp. 2d 1040, 1060–61 (S.D. Ind. 2010) (Hamilton, J.) (allowing expert's causation opinion

based on non-epidemiological sources where epidemiological studies were scarce); *cf. Norris v. Baxter Healthcare Corp.*, 397 F.3d 878, 882 (10th Cir. 2005) (noting that epidemiological studies are not always necessary but that where "there is a large body of contrary epidemiological evidence, it is necessary to at least address it"). In this case, because Dr. Rinder adequately addresses the few epidemiological studies at issue and presents alternative evidence, as discussed below, the Court is satisfied that his opinion is sufficiently reliable to be admissible despite the fact that he has limited epidemiological evidence in his favor.

Having criticized the relevant observational studies, Dr. Rinder bases his opinion primarily upon clinical data, case reports, adverse event reports, and the evidence of biological plausibility. In terms of clinical data, Dr. Rinder relies upon a letter to the editor written by L. Xu and C.M. Schooling, in which the authors report the results of a meta-analysis of clinical trials. In the letter, the authors report a statistically significant association between TRT and VTEs, with a confidence interval of 1.39–22.8. Dr. Rinder also relies heavily on an analysis of case reports, which he argues demonstrates that TRT heightens the risk of VTE; VTE can occur rapidly after starting TRT; and many men who are predisposed to VTEs because of an inherited risk factor (such as Factor V Leiden mutation) might not develop a VTE until they are exposed to TRT. AbbVie offers substantive criticisms of both the Xu and Schooling letter and of the case studies on which Dr. Rinder relies. But as discussed above, at this stage, it is not the Court's role to choose among studies. *Schultz*, 721 F.3d at 433. AbbVie also argues that an opinion based on case reports and other data such as adverse event reports is unreliable. But the cases on which AbbVie relies suggest that case reports and other

non-epidemiological data are not reliable as the *sole* source of scientific evidence. *See, e.g.*, *Casey v. Ohio Med. Prod.*, 877 F. Supp. 1380, 1385 (N.D. Cal. 1995) (discussing unreliability of case studies alone because they do not consider potential alternative causes or investigate mechanisms of causation). In this case, however, Dr. Rinder considers multiple forms of evidence in forming his opinion. Though studies of case reports are considered less reliable than epidemiological studies, in a case such as this, "such studies may be carefully considered in light of other information available." *Tucker*, 701 F. Supp. 2d at 1062.

In considering the totality of the evidence to form his opinion, Dr. Rinder extensively discusses the biological plausibility of his proposed mechanisms. AbbVie takes issue with his analysis of each mechanism. In addition to its criticism of his reliance on animal studies, an issue the Court addressed earlier, AbbVie challenges Dr. Rinder's opinion that elevated hematocrit levels from TRT use can cause VTEs because he reports the results of a study finding that men with hematocrit levels above or equal to 46% had a greater than 2-fold increase in VTE risk compared with men whose hematocrit levels were below 43%. Dr. Rinder's reliance on this study makes his opinion regarding hematocrit unreliable, AbbVie argues, because 46% is below the upper bound of the normal range of hematocrit levels for men. Thus the study, according to AbbVie, flies in the face of accepted medicine. In addition, AbbVie argues, it is inappropriate to draw conclusions about TRT from the study because the study did not involve TRT. The Court disagrees that these concerns render Dr. Rinder's hematocrit opinion unreliable. AbbVie has not demonstrated that the upper range for a normal hematocrit level is based on VTE risk, such that Dr. Rinder's opinion would be in

conflict with current medical practice. And AbbVie has not explained why Dr. Rinder should not be permitted to draw a conclusion about the effects of increased hematocrit on VTEs, irrespective of the cause of that increase, given other evidence that TRT does increase hematocrit.

AbbVie's criticism of the opinions of Drs. Rinder and Halushka regarding the proposed mechanism of increased thromboxane A2 receptors is largely based on their use of animal studies, an issue which the Court addressed earlier. AbbVie also criticizes Dr. Rinder for declaring that "[p]latelet effects of testosterone have been confirmed in humans" without citing any supporting evidence. But in the same paragraph where Dr. Rinder makes that assertion, he cites to two studies, the titles and abstracts of which suggest they demonstrate platelet effects in human cell lines and in human beings *in vivo*. *See* Rinder Rep. [dkt. no. 1812-9] at 13. In addition, AbbVie suggests that Dr. Halushka's proposed testimony will not assist the trier of fact because he "simply discusses how platelet aggregation plays a role in VTE development—which is obvious because VTEs are blood clots formed by platelets (as opposed to the white blood cells that clot and cause [myocardial infarctions] and strokes)." Defs.' Br. at 97. The problem with this argument is that the statement following the word "obvious" is contradicted by AbbVie's own expert, Dr. Sucha Nand, who explains that clots in the veins are characterized by having more red blood cells (not platelets), whereas *platelets* (not white blood cells) primarily form the arterial clots that cause heart attacks and strokes. Nand Rep., Ex. 4 to Defs.' Mot., at 4–5. Given this apparent confusion about the role of platelets in VTE development, the Court is not persuaded that Dr. Halushka's proposed testimony is obvious or will be unhelpful to the trier of fact.

AbbVie also argues that other flaws in Dr. Rinder's methodology require the exclusion of his testimony. AbbVie contends that Dr. Rinder applies different standards when evaluating whether non-TRT risk factors are causal versus whether TRT is causal. The Court disagrees. During his deposition, Dr. Rinder adequately explained the criteria by which he assesses whether a risk factor is causal. He acknowledges that the well-established inherited risk factors are causal because there is a scientific consensus regarding their relationship to VTEs. TRT, on the other hand, does not have such a consensus, but Dr. Rinder explains that such a consensus is lacking because TRT use has only recently expanded and been the subject of attention and study. Dr. Rinder also explains that he is less confident in the causal status of VTE risk factors other than TRT that are not well-established because he is skeptical of the plausibility of their biological mechanism and of the lack of data supporting their causal role. Whether or not AbbVie agrees with the standard Dr. Rinder applies for making such assessments, or whether it is the correct standard, it is a reasoned and principled one.

According to AbbVie, Dr. Rinder's general causation opinion is unreliable because he uses the methodology of differential diagnosis, which is an inappropriate method for establishing general causation. The Court discusses differential diagnoses below. AbbVie's argument that Dr. Rinder relies on a differential diagnosis to form his general causation opinion is simply not supported. His opinion does not rely on the exclusion of potential causes, as one does when conducting a differential diagnosis. Rather, he analyzes studies of various sorts, assesses the weight to accord to different pieces of evidence, and considers the plausibility of the proposed biological mechanisms. This is not a differential diagnosis, and for the reasons discussed above,

the Court concludes that it is an adequately reliable basis for his opinion that TRT, in general, is a cause of VTE injuries.

3. Specific causation

a. Differential diagnosis or etiology

To establish that AndroGel was a "significant contributing factor" to each plaintiff's alleged injury, plaintiff's specific-causation experts purport to apply the same methodology: differential diagnosis. There is no dispute that a differential diagnosis, also referred to more accurately in this context as a "differential etiology,"[13] is a reliable methodology for making a specific-causation determination. *See Schultz*, 721 F.3d at 433 (differential diagnosis and differential etiology are "generally accepted means for evaluating the cause of a plaintiff's injury"). But "an expert must do more than just state that she is applying a respected methodology, she must follow through with it." *Brown v. Burlington N. Santa Fe Ry. Co.*, 765 F.3d 765, 773 (7th Cir. 2014). When conducting a differential etiology, an expert "rules in all the potential causes of a patient's ailment and then by systematically ruling out causes that would not apply to the patient, the [expert] arrives at what is the likely cause of the ailment." *Myers*, 629 F.3d at 644. An expert is not required to rule out every alternative cause. *Schultz*, 721 F.3d at 434. But where reasonable alternative causes exist, the expert should explain why he does not believe the alternatives were the sole cause of the plaintiff's injury. *Id.*

AbbVie maintains that each of plaintiffs' specific-causation experts failed to apply

[13] Though the terms are often used interchangeably, they have different technical meanings. Medical doctors perform differential diagnoses in clinical settings to determine the disease or condition from which a patient is suffering. A differential etiology, on the other hand, seeks to determine "not what [a patient or plaintiff] is suffering from, but what *caused* his ailments." *Myers*, 629 F.3d at 644 (emphasis added).

the differential etiology method in a reliable manner. For the reasons stated in this section, the Court disagrees and concludes that, with the exception of Dr. Setaro's purported differential etiology in Cribbs's case, plaintiffs' experts reliably applied the method of a differential etiology.

As an initial matter, AbbVie argues that plaintiffs' experts lack a valid basis for "ruling in" AndroGel as a potential cause of plaintiffs' injuries because, according to AbbVie, (1) plaintiffs have failed to establish in general that AndroGel is a recognized cause of their alleged injuries and (2) plaintiffs do not fit into any subpopulations (based on, for example, age and duration of use) for which a statistically significant association has been reported. As discussed above, however, the Court concludes that plaintiffs' experts have a reliable basis to opine that AndroGel is capable of causing the alleged injuries in the population of TRT users at large. Thus plaintiffs' experts are justified in relying on one or more of plaintiffs' general-causation expert reports to rule in AndroGel as a potential cause of plaintiffs' injuries.

AbbVie also criticizes plaintiffs' experts for failing to properly consider and rule out alternative causes as potential sole causes of plaintiffs' injuries. Specifically, AbbVie argues that plaintiffs' experts were required to quantify the risks posed by each alternative cause that they could not definitively rule out. The Court disagrees that such quantification is required to reliably conduct a reliable differential etiology. It is true that where numerous causes of an injury are plausible, an expert may not "simply pick[] the cause that is most advantageous to [the plaintiff's] claim." *Viterbo v. Dow Chem. Co.*, 826 F.2d 420, 424 (5th Cir. 1987). Quantifying the risks posed by alternative causes is, of course, one way to establish that a particular risk was a likely cause of the plaintiff's

injury. But under Seventh Circuit law, in a case like this, the expert's task is to provide a reliable basis for concluding that the drug at issue was a "substantial factor" in the development of the plaintiff's injury and that the other potential causes are unlikely to have been the injury's sole cause. *See Schultz*, 721 F.3d at 433. Quantifying the risks of alternative causes is not required.

In the cases AbbVie cites for the proposition that an expert must quantify the risks of potential causes, the particular factual circumstances were such that failure to quantify the risks of alternative causes left the experts with little to no basis for their specific-causation opinion. *See McDowell v. Brown*, 392 F.3d 1283, 1301–02 (11th Cir. 2004) (expert's theory that prisoner would have suffered lesser injury had he been treated earlier was not based on empirical evidence, quantification of effect delay had on prisoner's condition, or any other reliable method of proof); *Haller v. AstraZeneca Pharm. LP*, 598 F. Supp. 2d 1271, 1287–88 (M.D. Fla. 2009) (expert conceded that, given plaintiff's risk factors, plaintiff would have developed diabetes whether or not he took drug and that expert could not quantify the extent to which use of drug would accelerate onset of diabetes); *Magistrini v. One Hour Martinizing Dry Cleaning*, 180 F. Supp. 2d 584, 610 (D.N.J. 2002) (expert who discounted smoking entirely as risk factor for leukemia in expert report conceded at *Daubert* hearing that smoking is a risk factor but did not address relative weight of that risk or otherwise support his decision to stand by his initial causation opinion). As discussed in greater depth below, in the majority of the bellwether cases, plaintiffs' experts point to particular aspects of each plaintiff's case that provide an adequate basis for concluding that AndroGel was a substantial contributing factor to his injuries and that potential alternatives were unlikely to be the

sole causes of the injury.

An expert's causation opinion is also unreliable, according to AbbVie, if it is based solely on the temporal proximity between exposure to AndroGel and the cardiovascular event or VTE the plaintiff suffered. It would, of course, be a mistake to find a causal relationship "simply because a person takes drugs and then suffers an injury." *McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1243 (11th Cir. 2005). But that does not mean that the temporal proximity of exposure to a drug and a subsequent injury is irrelevant to a causation analysis. In one of the cases on which AbbVie relies, the court explained that although temporal proximity may be probative evidence in certain cases, the particular circumstances of that case made it unreliable. *See Guinn v. AstraZeneca Pharm. LP*, 602 F.3d 1245, 1254 (11th Cir. 2010). In *Guinn*, for example, the plaintiff alleged that a prescription antipsychotic drug caused him to gain weight, which led to the development of diabetes. Because both weight gain and the development of diabetes take place over long periods of time and can be the product of multiple causes, the fact that the plaintiff developed diabetes four years after beginning to take the drug shed little light on whether the drug was the cause of his weight gain and whether that weight gain was the cause of his diabetes. *Id.* at 1254.

In this case, however, plaintiffs' proposed theories of mechanism linking the drug to the alleged injuries are more direct and allow for a shorter time between exposure and injury. Thus, given the circumstances of certain plaintiffs' cases, temporal proximity may have more probative value, especially in connection with other indicia of causation. *See Westberry v. Gislaved Gummi AB*, 178 F.3d 257, 265 (4th Cir. 1999) (temporal relationship probative of causation where plaintiff's sinus disease began shortly after

exposure to talc at workplace). In any event, as discussed below, none of plaintiffs' experts rely exclusively on temporal proximity to reach their conclusions, and thus their opinions are not unreliable on that basis.

AbbVie also suggests, in arguing that the testimony of some of the experts discussed below should be excluded, that an expert opining about specific causation must have evidence of the mechanism by which the particular plaintiff's injury was caused. The Court disagrees, however, that this is a requirement for a reliable causation opinion. Once the experts in this case have established that TRT is capable of causing the type of injury alleged, they need only provide some reliable explanation for why they believe AndroGel was a substantial factor in bringing about the injury. *See, e.g.*, *In re Gadolinium-Based Contrast Agents Prod. Liab. Litig.*, No. 1:08 GD 50000, 2010 WL 1796334, at *5 (N.D. Ohio May 4, 2010) ("Nothing in Rule 702, *Daubert* or the relevant case law requires experts to know the precise mechanical process underlying a cause when other evidence is sufficient to show causation.").

b. Dr. Ziman (plaintiff Frost)

Frost began using AndroGel 1.62% on January 11, 2012. There is a factual dispute about whether Frost used AndroGel continuously until he suffered a stroke beginning roughly on February 17, 2013, at the age of 59. In April 2012, Frost's prescribing physician, Dr. Christopher Chow, instructed him to increase the amount of gel he was taking. Although there is no medical record indicating that Dr. Chow instructed Frost to stop taking AndroGel, Dr. Chow did instruct Frost to resume taking AndroGel on January 23, 2013. In forming his opinion in this case, Dr. Ziman assumed that Frost had stopped taking AndroGel but resumed taking it in January 2013.

Dr. Ziman acknowledged that Frost had multiple risk factors for stroke other than his use of AndroGel, including his age, race (African American), hypertension, type 2 diabetes, dyslipidemia (abnormal lipid levels in the blood), history of smoking cigarettes, excessive alcohol use, body weight (overweight but not obese), and positive family history (mother and one sister with history of heart attack, one sister with history of stroke). In forming his opinion, Dr. Ziman determined, on the basis of Frost's medical records and images, that the stroke was embolic in nature—and was not the result of a cardiac embolism or hemorrhaging—and was thus the type of stroke one might expect to result from a drug that enhances the pro-thrombotic state, as AndroGel purportedly does. In addition, Dr. Ziman concluded that AndroGel was a likely cause of Frost's injury, as compared to his other risk factors, because (1) it was not until soon after Frost took AndroGel, and immediately after he resumed taking AndroGel that he suffered his stroke, despite his long-standing risk factors; (2) he did not have any areas of significant vessel narrowing that would predispose him to an ischemic stroke; and (3) in the four years since he has discontinued AndroGel use, he has not had any recurrence of a transient ischemic attack. Based on this analysis, the Court concludes that Dr. Ziman has a reliable basis for concluding that AndroGel was a substantial factor in causing Frost's stroke and that the other risk factors mentioned by AbbVie and in Dr. Ziman's report are unlikely to be the sole cause of his injury.

AbbVie also maintains that Dr. Ziman's opinion is unreliable because he assumes that Frost was continuing to use AndroGel at the time of his stroke, an assumption AbbVie argues is contradicted by the evidence. The Court disagrees that the accuracy of Dr. Ziman's assumption should affect the admissibility of his opinion. As

plaintiffs point out, where "a medical expert has relied upon a patient's self-reported history and that history is found to be inaccurate, district courts usually should allow those inaccuracies in that history to be explored through cross-examination." *Walker v. Soo Line R.R. Co.*, 208 F.3d 581, 586 (7th Cir. 2000). It will be the jury's role to determine whether Dr. Ziman's assumptions were correct and whether the ultimate conclusion he draws is accurate.

c. Dr. Cuculich (plaintiff Konrad)

Konrad first purchased an AndroGel 1% pump on May 5, 2010, roughly two months before he suffered a myocardial infarction on July 8, 2010, at the age of 49. His risk factors for cardiovascular injury prior to his heart attack included a family history (grandfather who died from heart attack at age 65), dyslipidemia, and obesity. Dr. Cuculich explains in his report why Konrad's other health conditions, including atrial fibrillation, "fatty liver," and hypothyroidism, are not risk factors for myocardial infarction. AbbVie argues that Dr. Cuculich failed to apply a reliable differential etiology because he did not rule out Konrad's poor cholesterol levels, high triglyceride levels, or hypertension as causes of Konrad's myocardial infarction. Dr. Cuculich, however, did consider those risks and expressly calculated Konrad's cardiovascular risk, apart from his AndroGel usage, determining that he was at low risk for atherosclerotic cardiovascular disease and heart attack. Dr. Cuculich also determined that the sudden nature of the onset of Konrad's symptoms and the description of the plaque in his coronary artery was consistent with a rupture of a coronary artery plaque that resulted in a thrombus forming at that location and blocking blood flow to the heart. Such an injury is the type one would expect based on Dr. Cuculich's theory of the mechanism by which

TRT causes heart attacks. Ultimately, Dr. Cuculich concluded that the absence of other significant cardiovascular risks, combined with the recent initiation of TRT, indicated that AndroGel was a substantial contributing factor in causing Konrad's heart attack. Based on a review of Dr. Cuculich's report, the Court concludes that he provided adequate reasons for his determination that Konrad's alternative risk factors were not the sole cause of his heart attack and the AndroGel was a substantial contributing factor to Konrad's injury.

d. Dr. Ardehali (plaintiff Mitchell)

Mitchell started taking AndroGel in December 2007. He suffered a severe heart attack in November 2012. In his report concerning Mitchell, Dr. Ardehali acknowledges that Mitchell possessed the following risk factors for atherosclerotic cardiovascular disease: hypertension, dyslipidemia, positive family history, and active smoking. Though Dr. Ardehali did not rule these risk factors out as potential causes of Mitchell's heart attack, he does explain in his report why he believes they did not constitute the sole cause of the particular myocardial infarction Mitchell suffered. Dr. Ardehali acknowledges that risk factors other than AndroGel were integral in the formation of the lesions that were found on Mitchell's artery. But Dr. Ardehali explains why, under his theory of the mechanism by which TRT causes cardiovascular injuries, AndroGel played a significant role in causing the "acute thrombotic event" that led to Mitchell's ultimate injury. According to Dr. Ardehali, it is the pro-thrombotic effects of TRT that can provoke such events in patients like Mitchell who have already developed atherosclerosis as a result of longstanding risk factors. Thus, although AbbVie has ample grounds to dispute Dr. Ardehali's conclusion that AndroGel was a substantial

factor in causing his injury, as opposed to his other well-documented risk factors, Dr. Ardehali has provided an adequate "link between the facts or data [he] has [reviewed] and [his] conclusion" that AndroGel played a substantial role in causing the injury. *United States v. Mamah*, 332 F.3d 475, 478 (7th Cir. 2003).

e. Dr. Rinder (plaintiffs Myers, Nolte, and Rowley)

Dr. Rinder offers specific-causation opinions in the cases of Myers, Nolte, and Rowley. Before discussing the particular risk factors and injuries suffered by each of those plaintiffs, the Court addresses certain general criticisms AbbVie launches against Dr. Rinder's specific-causation opinions.

AbbVie argues that Dr. Rinder's specific-causation opinions are unreliable because he fails to quantify the plaintiffs' risk factors in forming his opinions. As discussed earlier, the Court does not agree that such quantification is necessary as long as an expert provides some reliable basis for concluding that the alternative risk factors that cannot be ruled out are unlikely to be the sole cause of the plaintiff's injury. In addition, in the cases he addresses, Dr. Rinder actually assigns relative weights to the plaintiffs' various risk factors and identifies particular features of each plaintiff's case that indicate AndroGel was a substantial contributing factor to the injury.

AbbVie also faults Dr. Rinder for failing to define "substantial contributing factor." But there is no reason to believe that that term has any meaning other than its common everyday usage, and Dr. Rinder's failure to provide a definition goes to the weight to be given to his conclusion that AndroGel is such a factor, not to the admissibility of his opinion.

In addition, AbbVie criticizes Dr. Rinder for concluding that AndroGel was a

cause of each plaintiff's VTE even though only Nolte had an above-normal hematocrit level. In Dr. Rinder's general expert report, however, he offers other plausible mechanisms besides increased hematocrit, such as increased estradiol and thromboxane A2 receptors. Dr. Rinder's general causation opinion also provides some support for the notion that increased hematocrit can cause VTE injuries even if the absolute level does not exceed the normal range. In any event, as discussed earlier, an expert need not identify the precise mechanism of causation when performing a differential diagnosis. Dr. Rinder's failure to identify the mechanism at work for each plaintiff goes to the weight his opinion should be afforded, not its admissibility.

Myers was diagnosed with a pulmonary embolism in February 2008 at the age of 43. He first began using AndroGel in May 2003 and was using the drug at the time of his VTE. His medical history indicates that he has a positive family history of VTEs, as both his father and sister suffered from DVTs. At the time of his pulmonary embolism, Myers was also morbidly obese, had elevated hemoglobin A1c levels (indicating insulin resistance) and blood lipid levels, suffered from sleep apnea, and had recently taken a trip to Jamaica on an airplane. Dr. Rinder considered each of these factors in forming his opinion that AndroGel was a substantial factor in bringing about Myers' pulmonary embolism. Dr. Rinder notes in his report that Myers' blood work did not detect any inherited and acquired VTE risk factors, and Dr. Rinder explains why he considers Myers' other apparent risk factors to be either weak risk factors or not risk factors at all for VTE. Dr. Rinder testified that he considered Myers' family history to be a relatively weak factor because his family members' DVTs could be explained by their particular circumstances, such as the sister's neurologic disorder and the father's old age at the

time of his DVT. In his report, Dr. Rinder also discounts the risk posed by Myers' flight to Jamaica because it was a relatively short flight, broken into segments, whereas increased VTE risk is usually attributed only to "long haul" air travel. Dr. Rinder also assigned little weight to Myers' hyperlipidemia, insulin resistance, or sleep apnea as potential causes of his injury because although those some of those conditions are associated with other risks, such as increased rate of cardiovascular events, he did not consider them to be traditionally recognized or clinically relevant risk factors for VTEs. Finally, Dr. Rinder acknowledged that Myers' morbid obesity increased his VTE risk but explains that he does not believe it to be a sufficient risk to rule out AndroGel as a cause, especially given the way that VTE risk factors act synergistically. The Court thus concludes that Dr. Rinder adequately accounted for each of Myers' potential VTE risk factors and explained sufficiently why he did not believe they were the sole cause of the pulmonary embolism Myers suffered.

Nolte suffered a pulmonary embolism in November 2012, at the age of 72, two months after he began using AndroGel. He had previously suffered a pulmonary embolism after undergoing coronary bypass surgery in early 2011, prior to taking AndroGel. In addition to his own personal VTE history, Nolte has a family history of VTEs: his mother suffered from a DVT, and his son had a pulmonary embolism. Both Nolte and his son tested positive for the inherited Factor V Leiden risk factor. Nolte's other potential VTE risk factors, which Dr. Rinder considered in forming his opinion, include diagnosed ulcerative colitis, being overweight, and a history of varicose veins. As in the case of Myers, Dr. Rinder considered Nolte's other co-morbid conditions—including hypertension, hypercholesterolemia, history of pancreatitis, and history of

bladder cancer—and explained that those conditions are not traditionally recognized or clinically relevant risk factors for VTE. Dr. Rinder similarly did not consider Nolte's non-recurring varicose veins or his being overweight, as opposed to being morbidly obese, to be significant VTE risk factors.

Regarding Nolte's personal and family history of VTEs, Dr. Rinder discounted the personal history of a pulmonary embolism because of its apparent connection to his surgery, and he determined that the family history was consistent with the presence of the factor V Leiden mutation. Ultimately, after ruling out causes, Dr. Rinder determined that Nolte's risk factors included the factor V Leiden mutation and ulcerative colitis. Dr. Rinder explained that these are relatively weak VTE risk factors but also noted the synergistic nature of VTE risk factors and the data from the case-report literature suggesting that TRT can increase the risk of VTEs in users who test positive for the factor V Leiden mutation. He emphasized that this synergistic effect is supported by reports of TRT users suffering VTEs even while being treated with anticoagulation therapy. Dr. Rinder provided ample explanation for his conclusion that AndroGel likely acted synergistically with the risk factors that Dr. Rinder could not rule out, and he therefore provided a reliable basis for his opinion that AndroGel contributed substantially to Nolte's development of a pulmonary embolism.

Rowley was 67 years old when his DVT was detected by ultrasound in late April 2013. At the time, he had been taking AndroGel for roughly one year. Concerned that AndroGel contributed to the development of his DVT, Rowley's treating physicians recommended discontinuing use of the drug. In forming his opinion that AndroGel substantially contributed to Rowley's injury, Dr. Rinder considered whether Rowley's

Crohn's disease, overweight status, history of superficial thrombophlebitis (clotting in veins near the surface of the skin), or other inherited or acquired risk factors contributed to the formation of Rowley's DVT. Dr. Rinder noted that there was no evidence that Rowley had any inherited or irreversible acquire VTE risk factors. Although he acknowledged that Crohn's disease is a VTE risk factor, Dr. Rinder explained that the increased risk from Crohn's disease can be attributed primarily to higher rates of hospitalization and surgery, as well as treatment with corticosteroids. Because those risk factors did not apply to Rowley, Dr. Rinder considered his Crohn's disease to be a weak risk factor at most. Dr. Rinder also ruled out weight as contributing factor because Rowley was not obese at the time of his injury, and he discounted Rowley's history of thrombophlebitis because his isolated episodes had been resolved four years prior to his VTE event. In ruling out other risk factors as the possible sole causes of Rowley's DVT, Dr. Rinder importantly noted that Rowley had previously undergone major abdominal surgery prior to starting AndroGel use without any VTE complications, suggesting that whatever risk factors were present prior to Rowley's use of AndroGel were unlikely to be a sole cause of his DVT. The Court is satisfied that Dr. Rinder adequately accounted for alternative causes and provided a reliable basis for his conclusion that AndroGel was a significant contributing factor to the development of Rowley's injury.

f. Dr. Setaro (plaintiff Cribbs)

Unlike plaintiffs' other specific-causation experts, Dr. Setaro fails to provide an adequate explanation for his conclusion that AndroGel, and not some other combination of causes, led to the plaintiff's injury. The bulk of Dr. Setaro's expert report is devoted to

a differential diagnosis, identifying the *type* of heart attack Cribbs suffered, as opposed to a differential etiology addressing the cause of the injury. Cribbs suffered his heart attack in May 2012 at the age of 61. He had used AndroGel for over two years prior to the heart attack. Dr. Setaro acknowledged that Cribbs had the following cardiovascular risk factors: age, gender, family history of cardiac disease (two sisters and a grandmother diagnosed with hypertension), obesity, elevated lipids, hypertension, diabetes, and a thirty-year history of smoking until 1999.

According to Dr. Setaro, Cribbs's medical history and the available medical imaging suggest that his heart attack was likely the result of a transient thrombotic occlusion. But Dr. Setaro's discussion in his report of the *cause* of that thrombotic event is brief and lacks adequate explanation. In his report, Dr. Setaro lists Cribbs's multiple cardiovascular risk factors and concedes that those factors "are known to promote vascular inflammation, and thereby to heighten the tendency toward athero-thrombotic events." Rep. of Dr. Setaro [dkt. no. 1812-15] at 9. After making that acknowledgment, however, Dr. Setaro simply concludes, abruptly, that the "presence of those risk factors does not exculpate testosterone." *Id.* According to Dr. Setaro, TRT was a substantial factor in promoting Cribbs's cardiovascular disease and his acute thrombotic syndrome "by its effect on coagulation under conditions of generalized systemic vascular inflammation." *Id.* But apart from this discussion of the mechanism by which AndroGel might contribute to increased cardiovascular risk, Dr. Setaro does not point to anything about Cribbs's case in particular to suggest that his injury was the result of AndroGel rather than the multiple other risk factors that Dr. Setaro was unable to rule out. Dr. Setaro also asserts that TRT's adverse effects are proportionately greater in Cribbs in

comparison to the rest of the population because of his other cardiovascular risk factors, but he does not cite to any medical support for this opinion. Essentially, Dr. Setaro's opinion boils down to a conclusion that because AndroGel is capable of causing heart attacks, he believes it contributed to Cribbs's heart attack, regardless of the other risk factors Cribbs had. One cannot, however, simply take Dr. Setaro's unsupported word that because AndroGel can cause heart attacks, it was a specific cause of Cribbs's injury. An opinion like this one that "amounts to nothing more than the *ipse dixit* of the expert" is not admissible. *Wood*, 807 F.3d at 837.

D. Summary judgment

In its motion for summary judgment on the issue of causation, AbbVie's sole argument for summary judgment is that plaintiffs lack admissible expert testimony on the critical element of causation. As discussed above, however, the Court concludes that plaintiffs' expert testimony regarding general causation is largely admissible and that testimony regarding specific causation is admissible in the cases of Frost, Konrad, Mitchell, Myers, Nolte, and Rowley. The Court therefore denies summary judgment in those cases, at least with respect to the question of whether plaintiffs' use of AndroGel caused the plaintiffs' injuries. The exclusion of Dr. Setaro's testimony, however, requires the Court to grant summary judgment in favor of AbbVie in Cribbs's case. Under North Carolina law, expert testimony is required to establish causation for the type of injury Cribbs alleges. *See Hensley v. Danek Med., Inc.*, 32 F. Supp. 2d 345, 350 (W.D.N.C. 1998) ("In North Carolina, a jury award [in a products liability case] cannot be sustained in the absence of expert medical testimony on the issue of causation."); *Holley v. ACTS, Inc.*, 357 N.C. 228, 232, 581 S.E.2d 750, 753 (2003) ("In cases

involving complicated medical questions far removed from the ordinary experience and knowledge of laymen, only an expert can give competent opinion evidence as to the cause of the injury.") (internal quotation marks omitted). Without admissible expert testimony on the issue of specific causation, Cribbs cannot prove his claims under North Carolina law.

Conclusion

For the reasons stated above, the Court denies plaintiffs' motion to limit the testimony of Dr. Marais [dkt. no. 1738], grants summary judgment in favor of AbbVie on the claims of plaintiff Edward Cribbs, and otherwise denies AbbVie's motion to exclude plaintiffs' expert testimony on the issue of causation, and for summary judgment [dkt. no. 1753].

MATTHEW F. KENNELLY
United States District Judge

Date: May 8, 2017